ORGANIC LETTERS

2013
Vol. 15, No. 23
5964–5966

Chiral Phosphoric Acid Catalyzed Enantioselective Desymmetrization of *meso*-Epoxides by Thiols

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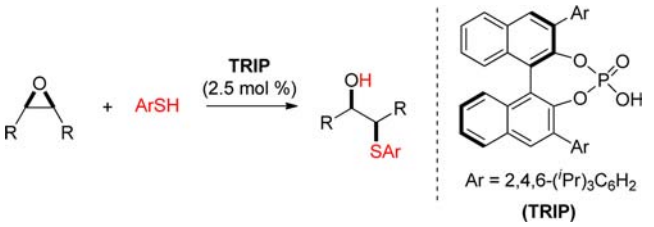
Received September 26, 2013

ABSTRACT



The first chiral Brønsted acid catalyzed asymmetric nucleophilic ring-opening reaction of *meso*-epoxides is described. In the presence of TRIP, a range of *meso*-epoxides could undergo smooth ring-opening reactions by aryl thiols with good efficiency and enantioselectivity.

Catalytic enantioselective desymmetrization of *meso* compounds is an important strategy in asymmetric synthesis.[1] Specifically, asymmetric nucleophilic ring opening of *meso*-epoxides has received considerable attention, because it is a straightforward and attractive strategy to access 1,2-difunctionalized chiral molecules with vicinal stereocenters from readily available inexpensive compounds (Scheme 1).[2] Thus, in the past few decades, various catalytic systems have been developed for asymmetric ring openings of *meso*-epoxides with a variety of nucleophiles, including azides, amines, alcohols, thiols, halides, etc.[3,4] While a wide range of Lewis acids (e.g., transition-metal complexes) and Lewis bases as well as enzymes have been demonstrated to be effective catalysts, however, chiral Brønsted acids, a class of versatile catalysts in a large number of asymmetric reactions, have not been utilized as successful catalysts for this transformation so far.[5,6] Herein, we report the first chiral Brønsted acid catalyzed

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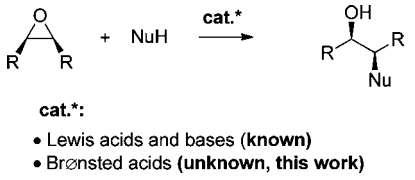
10.1021/ol402797v
Published on Web 11/12/2013

Scheme 1. Nonenzymatic Asymmetric Nucleophilic Ring Openings of *meso*-Epoxides



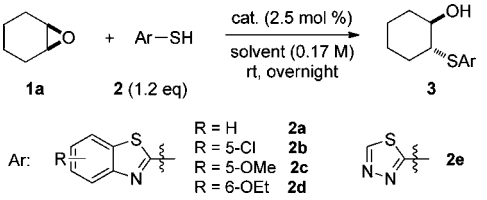
nonenzymatic asymmetric nucleophilic ring-opening reaction of *meso*-epoxides.

Inspired by the recent success of chiral phosphoric acid catalyzed desymmetrization reactions,[7−9] particularly by progress in oxetane and aziridine desymmetrization reactions,[10] we envisaged that chiral phosphoric acids should be suitable for epoxide activation toward subsequent stereocontrolled nucleophilic substitution.[11]

We began our study with cyclohexene oxide **1a** as the model substrate. Initial evaluation of common nucleophiles, e.g., BnOH, PhOH, $PMPNH_2$, $BnNH_2$, PMPSH, PMBSH, revealed that no reaction was observed in the presence of a catalytic amount of a typical chiral phosphoric acid. Next, we turned our attention to 2-mercaptobenzothiazole (**2a**), which is an excellent nucleophile in oxetane-opening reactions (Table 1).[10b] To our delight, the reaction with **1a** and **2a** proceeded smoothly at room temperature in toluene to form the desired product **3**. All the chiral phosphoric acids, except **B**, give full and clean conversion with a catalyst loading as low as 2.5 mol %. Among them, the BINOL-based catalyst **A2** (also known as TRIP) exhibited the best chiral induction (44% ee, entry 2). Next, we compared various substituted mercaptobenzothiazole and 1,3,4-thiadiazole-2-thiol nucleophiles with the **A2** catalyst (entries 9−13). The use of DCM as the solvent for this comparison was due to the poor solubility of some nucleophiles/products in toluene. The enantioselectivity could be improved with 5-methoxymercaptobenzothiazole (**2c**). Other solvents did not improve the selectivity further. After considerable effort in evaluating additives and reaction temperature (see SI for details), we finally found that the reaction could proceed at −78 °C with both excellent conversion and good enantioselectivity (entry 18).

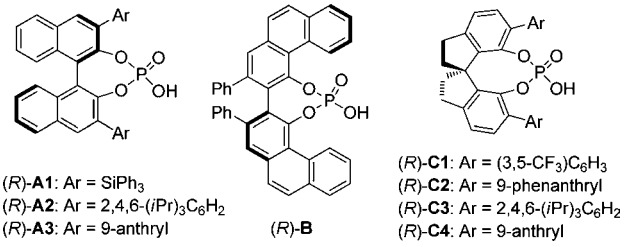
With the optimized conditions, next we examined the reaction scope. As shown in Table 2, a range of cyclic

Table 1. Condition Optimization[a]



entry	cat.	Ar−SH	solvent	ee (%)
1	(*R*)-**A1**	**2a**	toluene	40
2	(*R*)-**A2**	**2a**	toluene	44
3	(*R*)-**A3**	**2a**	toluene	9
4	(*R*)-**B**	**2a**	toluene	4
5	(*R*)-**C1**	**2a**	toluene	−18
6	(*R*)-**C2**	**2a**	toluene	−20
7	(*R*)-**C3**	**2a**	toluene	−31
8	(*R*)-**C4**	**2a**	toluene	−29
9	(*R*)-**A2**	**2a**	CH_2Cl_2	45
10	(*R*)-**A2**	**2b**	CH_2Cl_2	55
11	(*R*)-**A2**	**2c**	CH_2Cl_2	61
12	(*R*)-**A2**	**2d**	CH_2Cl_2	43
13	(*R*)-**A2**	**2e**	CH_2Cl_2	47
14	(*R*)-**A2**	**2c**	THF	55
15	(*R*)-**A2**	**2c**	EtOAc	57
16	(*R*)-**A2**	**2c**	cyclohexane	53
17[b]	(*R*)-**A2**	**2c**	CH_2Cl_2	73
18[c]	(*R*)-**A2**	**2c**	CH_2Cl_2	85

[a] Full conversion for all the entries, except entry 4, based on GC analysis with *n*-decane as an internal standard. [b] Run at −20 °C. [c] Run at −78 °C.



(6) For a Brønsted acid catalyzed intramolecular elimination, rather than intermolecular nucleophilic substitution, see: Dickmeiss, G.; De Sio, V.; Udmark, J.; Poulsen, T. B.; Marcos, V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6650–6653.

(7) Recent reviews on chiral phosphoric acid catalysis: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *248*, 999–1010. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (c) Terada, M. *Chem. Commun.* **2008**, 4097–4112. (d) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31–39. (e) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395–456. (f) Terada, M. *Synthesis* **2010**, 1929–1982. (g) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350–9365. (h) Yu, J.; Shi, F.; Gong, L. *Acc. Chem. Res.* **2011**, *44*, 1156–1171. (i) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539–4549. (j) Čorić, I.; Vellalath, S.; Müller, S.; Cheng, X.; List, B. *Top. Organomet. Chem.* **2013**, *44*, 165–194.

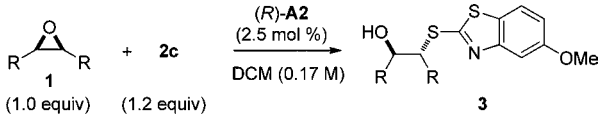
(8) For examples of chiral phosphoric acid catalyzed desymmetrization reactions, see: (a) Müller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534–18437. (b) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498–7499. (c) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057. (d) Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554–13557. (e) Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8572–8574. (f) Qabaja, G.; Wilent, J. E.; Benavides, A. R.; Bullard, G. E.; Petersen, K. S. *Org. Lett.* **2013**, *15*, 1266–1269. (g) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652–9654. (h) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964–3970.

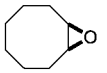
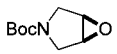
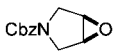
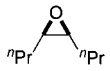
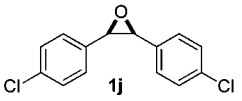
(9) For chiral phosphoric acid catalyzed desymmetrization of aziridines, see: (a) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084–12085. (b) Larson, S. E.; Baso, J. C.; Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 5186–5189. (c) Sala, G. D.; Lattanzi, A. *Org. Lett.* **2009**, *11*, 3330–3333.

(10) (a) Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2027–2031. (b) Wang, Z.; Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6685–6688. (c) Chen, Z.; Wang, Z.; Sun, J. *Chem.—Eur. J.* **2013**, *19*, 8426–8430.

(11) During the preparation of our manuscript, an asymmetric rearrangement of racemic epoxides catalyzed by chiral phosphoric acids was reported: Zhuang, M.; Du, H. *Org. Biomol. Chem.* **2013**, *11*, 1460–1462.

Table 2. Reaction Scope



entry	*meso*-epoxide (**1**)		temp (°C)	product	yield (%)[a]	ee (%)
1		**1a**	–78	**3a**	98	85
2		**1b**	–78	**3b**	96	80
3		**1c**	–78	**3c**	97	73
4[c]		**1d**	rt	**3d**	65	55
5[c]		**1e**	–40	**3e**	63	84
6[c]		**1f**	–40	**3f**	52	84
7[c]		**1g**	–40	**3g**	72	82
8		**1h**	–78	**3h**	94	76
9[c]		**1i**	–20	**3i**	98	74
10[c]		**1j**	rt	**3j**	60	46 (96)[b]

[a] Isolated yield. [b] The ee value in the parentheses is after recrystallization once. [c] 5 mol % of (*R*)-**A2** was used.

epoxides with different ring sizes and acyclic epoxides can all participate in the desymmetrization reaction with **2c** to form the desired products **3** with moderate to good efficiency and enantioselectivity. It is noteworthy that cyclooctene oxide (**1d**) and diaryl-substituted epoxides (**1i**–**j**) were also suitable substrates at an elevated temperature, considering that their low reactivity was reported.[2a,12] The mild reaction conditions can tolerate a range of functional groups, such as alkenes, protected amines, ethers, aryl halides, etc. The enantioselectivity could also be improved significantly after crystallization for solid products, e.g., **3j** (entry 10).

Although benzothiazole-based thiols are the only suitable nucleophiles for the enantioselective desymmetrization, these thioether products are useful precursors of versatile chiral building blocks. For example, the methoxybenzothiazole moiety in the desymmetrization product **3a** could be efficiently cleaved to form free thiol **4** with no erosion in enantiomeric excess (Scheme 2). This transformation significantly expands the scope and utility of the desymmetrization reaction.

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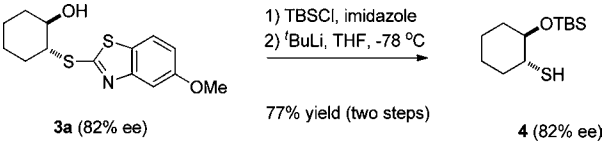
(13) Rai, A. K.; Singh, R.; Singh, K. N.; Singh, V. B. *Spectrochim. Acta, Part A* **2006**, *63*, 483–498.

Scheme 2. Transformation of **3a** to Free Thiol **4**



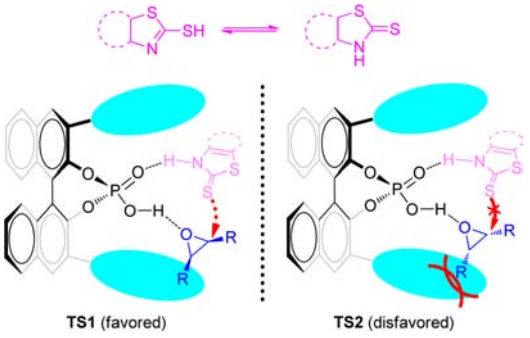


Figure 1. Possible transition states.

To rationalize the chiral induction mechanism of the asymmetric ring-opening process, we have proposed possible transition states (Figure 1). We believe that the epoxide is activated by the chiral acid moiety, and the nucleophile (presumably in its tautomer form)[13] is activated by the phosphoryl oxygen. In **TS1**, the epoxide is oriented not only with minimal steric repulsion with the catalyst but also in a reachable distance from the nucleophile. In contrast, the epoxide and the catalyst have strong steric repulsion in **TS2**, thereby leading to a disfavored path. These rationalizations are consistent with the observed product absolute stereochemistry.

In summary, the first chiral Brønsted acid catalyzed asymmetric nucleophilic ring-opening reaction of *meso*-epoxides has been realized. In the presence of a chiral phosphoric acid, a range of cyclic and acyclic *meso*-epoxides could undergo smooth ring-opening reactions with moderate to high efficiency and enantioselectivity. The mild reaction conditions can tolerate a range of functional groups. The enantioenriched 1,2-difunctionalized products with vicinal stereocenters are versatile chiral building blocks toward useful molecules, such as chiral free thiols.

Acknowledgment. Financial support was provided by HKUST and Hong Kong RGC (GRF-604411 and ECS-605812 to J.S. as well as the Hong Kong PhD fellowship to Z.W.).

Supporting Information Available. Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.